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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,217	03/02/2004	Els A.J.M. Goulmy	2183-4285.1US	3284

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,217	GOULMY ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/13/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19 and 21-25 are pending.

2. Claims 1-11 and 21 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 10/20/04, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any "suicide gene" for the claimed process.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo. The specification further discloses a process of ex vivo induction of HA-I and HA-2 specific CTLs wherein the method comprises pulsed APC with HA- 1or HA-2 peptides, cultured APC and responder cells (CD4 depleted autologous PBMC) in 24 well culture plates, restimulated the T cell cultures weekly with peptide pulsed autologous monocytes (page 26).

With the exception of the specific peptide, there is insufficient written description about the structure associated with function of any peptide "comprising" the sequence VLXDDLLEA (SEQ ID NO: 1) because the term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both end. Further, there is inadequate written description

about the structure of all "suicide gene" without the polynucleotide sequence for the claimed method of transducing the "suicide gene" into minor HA-1 antigen specific T cells.

The specification discloses only two peptides consisting of SEQ ID NO: 2 and 5 for a method of producing minor HA-1 antigen specific cytotoxic T cell, and only one suicide gene, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide for cytotoxic T cell against *all* minor antigen, and a representative number of species of "suicide gene" to describe the genus of peptide and "suicide gene" for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 6/13/05 have been fully considered but are not found persuasive.

Applicants' position is that claim 12 has been amended to refer peptide having up to 15 amino acids. The phrase "suicide genes" were well known to those skill in the art at the priority date of the present application and further elucidation would be unnecessary. One of such high skill would understand the meaning of the term "suicide gene". For instance, Goulmy et al, human immunology 54: 8-14, April 1997 (cited in Office Action at item 13), discloses the use of a suicide gene on page 12, lines 20-22. Further a well-known example of a suicide gene is a gene encoding the thymidine kinase of herpes simplex virus, which is identified and specifically referenced in the patent application at page 18, lines 6-8 of the specification as filed, i.e., cited reference 41 (Bonini, C. et al, Science 276: 1719-1724, 1997).

In response, the specification discloses only one suicide gene encoding the thymidine kinase of herpes simplex virus and cited reference 41 on page 20, paragraph 48. The disclosure fails to described any other suicide gene to be transduced into the cytotoxic T cell in the claimed process. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of "suicide gene" to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 12-18 and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: pulsing antigen presenting cells (APC) with the peptide consisting of SEQ ID NO: 1 wherein X represents histidine or arginine, coculturing said APC with CD4 depleted autologous PBMC, restimulating cytotoxic T cells weekly with the peptide and isolating minor antigen HA-1 specific cytotoxic T cells that are capable of HLA-A2.1 class I restricted VLHDDLLEA (SEQ ID NO: 2) or VLRDDLLEA (SEQ ID NO: 5) specific lysis of target cells.

Applicants' arguments filed 6/13/05 have been fully considered but are not found persuasive.

Applicants' position is that claim 12 has been amended to more clearly delineate steps of the claimed method (e.g., "pulsing an antigen presenting cell with the isolated, synthetic or recombinant peptide; and contacting a hematopoietic cell with the antigen cell, thus producing the cytotoxic T cells."

In response, the amended claim is still unclear how "hematopoietic cell" contacted with the antigen presenting cell suddenly becomes "cytotoxic T cells". One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 12-16, 18-19 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bakker et al (of record, Cancer Res 55(22): 5330-4, Nov 1995; PTO 892) in view of Goulmy et al (of record, Human Immunology 54: 8-14, April 1997; PTO 892) and Van der Haan et al (of record, Science 279(13): 1054-1.57, Feb 1998; PTO 1449).

Bakker et al teach a process of producing cytotoxic T cell against melanoma associated antigen, the process comprises providing peptide derived from melanocyte differentiation antigen to antigen presenting cells (APC) in the presence of peripheral blood monocytes (hematopoietic cell) and thus producing melanoma-associated antigen specific cytotoxic T cell in vitro or ex vivo (see abstract, in particular). Bakker et al teach CTLs are capable of recognizing naturally processed and presented epitopes and the ability to generate tumor peptide specific CTLs in vitro illustrates the potential used of these cells for vaccination protocols in human cancer (see abstract, in particular). The reference CTLs are capable of expansion in the presence of cytokines (see materials and methods, in particular).

The invention in claim 12 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen instead of melanocyte differentiation antigen by providing an isolated peptide having up to fifteen (15) amino acids and comprising the sequence VLXDDLLEA (SEQ ID NO: 1) wherein X represents histidine or arginine.

The invention in claim 13 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen wherein the hematopoietic cell is negative for the minor antigen.

The invention in claim 14 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen is HA-1.

The invention in claim 16 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen further comprises transducing the cytotoxic T-cell with a suicide gene.

The invention in claim 19 differs from the teachings of the reference only in that a cytotoxic T cell produced by the process according to claim 12.

Goulmy et al teach cytotoxic T cells specific for minor histocompatibility antigen such as HA-1 is useful for adoptive immunotherapy as a treatment by eliminating refractory, residual or relapsed leukemia in patient (see page 12, col. 1, in particular). Goulmy et al teach the ideal situation is to generate minor antigen HA-1 peptide CTLs ex vivo from minor antigen negative bone morrow donors for minor antigen positive patients (See page 12, col. 1, in particular). Goulmy et al further teach transduction of these CTLs with a suicide gene makes elimination of the CTL possible in case adverse effects occur (See page 12, col. 1, in particular).

Van der Haan et al teach minor histocompatibility antigen nanopeptides such as VLHDDLLEA and VLRDDLLEA that is 100 % identical to SEQ ID NO: 1 wherein X is histidine (H) or arginine (R) or about (see page 1056, col. 1, in particular) from HA-1 specific CTL clone (see page 1055, col. 3, in particular). Van der Haan et al further teach minor histocompatability HA-1 antigen comprising SEQ ID NO: 1 encoded by the cDNA sequence designated KIAA0223 (see page 1056, col. 1, in particular) as evident by GenBank accession number D86976.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute melanocyte differentiation antigen in the process for producing cytotoxic cell as taught by Bakker et al for the minor antigen HA-1 peptide such as VLHDDLLEA and VLRDDLLEA as taught by Van der Haan et al or the peptide as taught by Nagase et al for a method producing cytotoxic T cell against a minor antigen as taught by Bakker and Goulmy et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to produce cytotoxic T cell against minor antigen HA-1 because Goulmy et al teach cytotoxic T cells specific for minor histocompatibility antigen such as HA-1 can lyse leukemia cells expressing minor antigen and minor antigen specific CTL is useful for adoptive immunotherapy as a treatment by eliminating refractory, residual or relapsed leukemia in patient (see page 12, col. 1, in particular). Bakker et al teach CTLs are capable of recognizing naturally processed and presented epitopes and the ability to generate tumor peptide specific CTLs in vitro illustrates the potential used of these cells for vaccination protocols in human cancer (see abstract, in particular).

Applicants' arguments filed 6/13/05 have been fully considered but are not found persuasive.

Applicants' position is that Den Haan et al was published in Feb 1998. The priority documents were submitted in the parent (granted) patent application. Bakker, Goulmy, and Nagase et al do not disclose a peptide having up to 15 amino acids comprising XLXDDLLEA. Hence, any combination of Bakker et al, Goulmy and/or Nagase et al would not render the subject matter of current claims 12-21.

In response, the priority date of instant application is deemed to be the filing date of PCT/NL98/00424 filed 7/23/1998 because the foreign priority to application 97202303.0 filed 7/23/97 in the parent is not found. The Examiner apology for any inconvenience this may have cause to applicants. With regard to argument that Bakker, Goulmy, and Nagase et al do not disclose a peptide having up to 15 amino acids comprising XLXDDLLEA, the argument with respect to Nagase et al is moot since the Nagase reference used in this rejection has been dropped. However, Van der Haan et al teach minor histocompatibility antigen nanopeptides such as VLHDDLLEA and VLRDDLLEA that is 100 % identical to SEQ ID NO: 2 and SEQ ID NO: 5, respectively wherein X is histidine (H) or arginine (R) of claimed SEQ ID NO: 1 (see page 1056, col. 1, in particular) from HA-1 specific CTL clone (see page 1055, col. 3, in particular). Van der Haan et al further teach minor histocompatability HA-1 antigen comprising SEQ ID NO: 1 encoded by the cDNA sequence designated KIAA0223 (see page 1056, col. 1, in particular) as evident by GenBank accession number D86976.

11. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bakker et al (or record, Cancer Res 55(22): 5330-4, Nov 1995; PTO 892) in view of Goulmy et al (of record, Human Immunology 54: 8-14, April 1997; PTO 892), and Van der Haan et al (of record, Science 279(13): 1054-1057, Feb 1998; PTO 1449) as applied to claims 12-16, 18-19 and 23-24 mentioned above and further in view of Faller et al (J Virology 62(8): 2942-2950, August 1988; PTO 892).

The combined teachings of Bakker et al, Goulmy et al and Van der Haan et al and have been discussed supra.

The invention in claim 17 differs from the teachings of the references only in that a process for producing cytotoxic T cell against a minor antigen wherein the cytotoxic T cell is immortalized.

Faller et al teach a process of producing immortalized cytotoxic T cell by infecting cytotoxic T cells with HTLV-1 virus and prolong survival of CTL in vitro in the absence of

antigen stimulation without affecting the cytolytic capacity and antigen specificity of CTLs (see entire document, abstract, page 2943, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to immortalized any cytotoxic T cell as taught by Faller with the cytotoxic T cell against minor HA antigen as taught by Bakker et al, Den Haan et al, and Goulmy et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to immortalized cytotoxic T cell against minor antigen HA-1 because Faller et al teach that these T cell clones proliferated indefinitely in culture and retained their cytotoxic capacity and antigen specificity (see page 2942, col. 2, first paragraph, in particular). Goulmy et al teach cytotoxic T cells specific for minor histocompatibility antigen such as HA-1 can lyse leukemia cells expressing minor antigen and minor antigen specific CTL is useful for adoptive immunotherapy as a treatment by eliminating refractory, residual or relapsed leukemia in patient (see page 12, col. 1, in particular).

Applicants' arguments filed 6/13/05 have been fully considered but are not found persuasive.

Applicants' position is that any combination of Bakker et al, Goulmy and/or Nagase et al would not render the subject matter of current claims 12-21 (while Den Haan et al is not prior art to the present application). since claim 17 is dependent on inventive claim 12, claim 17 also involves an inventive step.

In response, the priority date of instant application is deemed to be the filing date of PCT/NL98/00424 filed 7/23/1998 because the foreign priority to application 97202303.0 filed 7/23/97 in the parent is not found. The Examiner apology for any inconvenience this may have cause to applicants. The rejection is maintain for the reasons of record.

12. The following new ground of rejection is necessitated by the amendment filed 6/13/05.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bakker et al (of record, Cancer Res 55(22): 5330-4, Nov 1995; PTO 892) in view of Goulmy et al (of record, Human Immunology 54: 8-14, April 1997; PTO 892), and Van der Haan et al (of record, Science 279(13): 1054-1057, Feb 1998; PTO 1449) as applied to claims 12-16, 18-19 and 23-24 mentioned above and further in view of Bonini et al (Science 276, 1719-1724, June 1997; PTO 892).

The combined teachings of Bakker et al, Goulmy et al and Den Haan et al and have been discussed supra. Goulmy et al further teach transduction of these CTLs with a suicide gene makes elimination of the CTL possible in case adverse effects occur (See page 12, col. 1, in particular).

The invention in claim 25 differs from the teachings of the references only in that the process for producing cytotoxic T cell against a minor antigen further comprising transducing the cytotoxic T-cell with a gene that codes for herpes simplex virus thymidine kinase.

Bonini et al teach a method of transducing suicide gene such as herpes simplex virus thymidine kinase into donor T cells to selectively eliminate and abrogate donor cells in the event of Graft versus host disease develops in patient (see page 1720, col. 1, particular). Bonini et al teach ganciclovir-mediated elimination of HSV-TK transduced cells was efficacious in the presence of acute GvHD (see page 1723, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the method step of transducing the cytotoxic T-cell with a gene that codes for herpes simplex virus thymidine kinase as taught by Bonini et al in the process of producing cytotoxic T cell against a minor histocompatibility antigen HA-1 peptide having up to

15 amino acids sequence as taught by Bakker et al, Goulmy et al and Van der Haan et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because transduction of these CTLs with a suicide gene makes elimination of the CTL possible in case adverse effects occur as taught by Goulmy et al (See page 12, col. 1, in particular). Bonini et al teach ganciclovir-mediated elimination of HSV-TK transduced cells was efficacious in the presence of acute GvHD (see page 1723, col. 2, in particular).

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

19. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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